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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/654,669	09/03/2003	Kirsty Spalding	21882-513 UTIL	5366

35437 7590 12/20/2005

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EXAMINER	
BERTAGNA, ANGELA MARIE	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 12/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/654,669	SPALDING ET AL.	
	Examiner	Art Unit	
	Angela Bertagna	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-31* is/are rejected.

7)☒ Claim(s) *1, 10, and 17* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 July 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 4/8/05
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Objections

1. Claim 1 is objected to because of the following informalities: step (c) is grammatically incorrect. The phrase "an birth date of said biomolecule" should be replaced with "a birth date...". Appropriate correction is required.

2. Claim 10 is objected to because of the following informalities: The claim has an extra period resulting in two sentences instead of a single sentence. Appropriate correction is required.

3. Claim 17 is objected to because of the following informalities: the use of the word "determine" instead of "determining" appears to be grammatically incorrect. Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claims 1-16 are indefinite, because claim 1 recites the limitation "said DNA" in step (c), line 2. There is insufficient antecedent basis for this limitation in the claim. For examination purposes, "said DNA" has been interpreted to mean "a biomolecule".

7. Claim 4 is indefinite, because "said biomolecule" is defined as "an animal, a plant, or a virus." A biomolecule is typically not considered to be an organism, but rather an organism is composed of biomolecules. Rewording the claim, perhaps by stating, "said biomolecule is derived from an animal, a plant, a virus" is suggested.

8. Claim 16 recites the limitations "said histone acetylation levels", "DNA oxidation levels", and "cellular lipofuschin levels" in lines 2-3. There is insufficient antecedent basis for this limitation in the claim, because these terms are not mentioned in the parent claim 14. In addition, this series (histone acetylation levels, DNA oxidation levels and cellular lipofuschin levels) lacks a conjunction (such as "and" or "or") making the scope of the claim further indefinite.

9. Claims 17-25 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: step (c) in the parent claim 17 where the step appears to be incomplete. For examination purposes, claim (c) has been interpreted as ending after the phrase "to determine a birth date of said biomolecule".

10. Claim 23 recites the limitation "said animal" in line 2. There is insufficient antecedent basis for this limitation in the claim, because an animal is not mentioned in the parent claim 17.

11. Claims 26-27 are indefinite, because claim 26 recites the limitation "said candidate compound" in step (b). There is insufficient antecedent basis for this limitation in the claim, because the claim appears to be directed to a "candidate agent".

Note that as defined in the specification an agent may be "materials, radiation, forces, fields, chemical compounds, etc. Since a candidate compound is only an example of a possible agent, the use of "candidate compound" in step (b) combined with "candidate agent" in step (c), renders the claims indefinite.

12. Claims 28-30 are indefinite, because claim 28 recites the limitations "said event" in step (b), "said first and second neuronal cell sample" in step (c), and "the neurological event" in step (d). There is insufficient antecedent basis for these limitations in the claim.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 1, 3-6, 11-13, 17-18, 22, and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Robertson et al. (Journal of Radioanalytical and Nuclear Chemistry, August 2001). As discussed in the 35 U.S.C. 112, second paragraph, rejection above, "said DNA" recited in step (c) of claim 1 lacks antecedent basis. Accordingly, claim 1 has been interpreted as a method of determining a birth date of any biomolecule, not limited to DNA.

With regard to claim 1, Robertson et al. teach a method for determining a birth date of a biomolecule comprising:

a. Providing a biomolecule (see abstract)

b. Determining a delta ^{14}C value of the biomolecule (page 445, 2nd paragraph)

c. Determining a birth date of said biomolecule by comparing the delta ^{14}C value of said biomolecule with a calibration delta ^{14}C chart to determine a birth date of said biomolecule (page 445, 2nd paragraph).

With regard to claim 3, the biomolecule of Robertson et al. is isolated from a tissue (Experimental section, page 444).

With regard to claim 4, the biomolecule of Robertson et al. originates from an animal, a plant, or a virus (page 444).

With regard to claim 5, the biomolecule of Robertson et al. is isolated from a purified cell population (Experimental section, page 444).

With regard to claim 6, Robertson et al. teach the use of a purified cell population that is a neuronal cell population (Experimental section, page 444).

With regard to claim 11, Robertson et al. determine the delta ^{14}C value using an accelerator mass spectrometer (page 445, 2nd paragraph).

With regard to claim 12, the calibration delta ^{14}C chart used by Robertson et al. is selected from a calibration delta ^{14}C chart shown in Figure 1 (see Figure 1 of Robertson et al. and page 445, 2nd paragraph).

With regard to claim 13, the delta ^{14}C chart is selected from the group consisting of a chart shown in Figure 1A, Figure 1B, Figure 1C, Figure 1D, and Figure 1E.

Specifically, Figure 1 of Robertson et al. corresponds to the instant Figure 1C (see page 444).

With regard to claim 17, Robertson et al. teach a method of determining the birth date of a biomolecule in an organism population, comprising:

(a) Collecting a sample of said biomolecule from an organism population; wherein said biomolecule is purified away from other carbon-containing molecules of said organism population (Experimental section, pages 444-445).

(b) determining a delta ^{14}C value of the carbon atoms in said biomolecule (page 445, 2nd paragraph)

(c) comparing the delta ^{14}C value with a calibration delta ^{14}C chart to determine a birth date of said biomolecule (page 445, 2nd paragraph).

With regard to claim 18, the organism (a human) used by Robertson et al. is an animal, a plant, or a virus (see abstract).

With regard to claim 22, Robertson et al. determine the delta ^{14}C value using an accelerator mass spectrometer (page 445, 2nd paragraph).

With regard to claim 31, Robertson et al. teach a method of determining a birth date of a biomolecule, comprising:

(a) providing a biomolecule (abstract)

(b) determining an isotope concentration of said biomolecule (page 445, 2nd paragraph)

(c) determining a birth date of said biomolecule by comparing the isotope concentration with a calibration isotope concentration chart to determine a birth date of said biomolecule (page 445, 2nd paragraph).

15. Claims 1-5, 7, 8, 11-13, 17-18, 22, 23, and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Wild et al. (Radiocarbon, 1998). As discussed in the 35 U.S.C. 112, second paragraph, rejection above, "said DNA" recited in step (c) of claim 1 lacks antecedent basis. Accordingly, claim 1 has been interpreted as a method of determining a birth date of any biomolecule, not limited to DNA.

With regard to claim 1, Wild et al. teach a method for determining a birth date of a biomolecule comprising:

a. Providing a biomolecule (see abstract)

b. Determining a delta ^{14}C value of the biomolecule (see abstract)

c. Determining a birth date of said biomolecule by comparing the delta ^{14}C value of said biomolecule with a calibration delta ^{14}C chart to determine a birth date of said biomolecule (see abstract).

With regard to claim 2, the biomolecule of Wild et al. is whole cell tissue (bone examples, Table 1, page 277).

With regard to claim 3, the biomolecule of Wild et al. is isolated from a tissue (lipids from bone marrow samples, Table 2, page 279).

With regard to claim 4, the biomolecule of Wild et al. originates from an animal, a plant, or a virus (see abstract).

With regard to claim 5, the biomolecule of Wild et al. is isolated from a purified cell population (see abstract).

With regard to claim 7, Wild et al. teach the use of dating hair samples which contain DNA, thereby meeting the limitation that the biomolecule is DNA (see abstract).

With regard to claim 8, Wild et al. teach that DNA is isolated from a tissue, a cell line or purified cell population, by removal of the hair from the skin tissue (see abstract).

With regard to claim 11, Wild et al. determine the delta ^{14}C value using an accelerator mass spectrometer (page 275).

With regard to claim 12, the calibration delta ^{14}C chart used by Wild et al. is selected from a calibration delta ^{14}C chart shown in Figure 1 (see Figure 1 of Wild et al., page 278).

With regard to claim 13, the delta ^{14}C chart is selected from the group consisting of a chart shown in Figure 1A, Figure 1B, Figure 1C, Figure 1D, and Figure 1E. Figure 1 of Wild et al. corresponds to the instant Figure 1B.

With regard to claim 17, Wild et al. teach a method of determining the birth date of a biomolecule in an organism population, comprising:

(a) Collecting a sample of said biomolecule from an organism population; wherein said biomolecule is purified away from other carbon-containing molecules of said organism population (see Methods section – Sample preparation, page 274).

(b) determining a delta ^{14}C value of the carbon atoms in said biomolecule (see Methods section – AMS measurements, page 275)

(c) comparing the delta ^{14}C value with a calibration delta ^{14}C chart to determine a birth date of said biomolecule (see Methods section – Age determination, pages 275-276).

With regard to claim 18, the organism (human) used by Wild et al. is an animal, a plant, or a virus (see abstract).

With regard to claim 19, Wild et al. teach the use of dating hair samples which contain DNA, thereby meeting the limitation that the biomolecule is DNA (see abstract).

With regard to claim 22, Wild et al. determine the delta ^{14}C value using an accelerator mass spectrometer (see Methods section – AMS measurements, page 275).

With regard to claim 31, Wild et al. teach a method of determining a birth date of a biomolecule, comprising:

(a) providing a biomolecule (abstract)

(b) determining an isotope concentration of said biomolecule (see Methods section – AMS measurements, page 275)

(c) determining a birth date of said biomolecule by comparing the isotope concentration with a calibration isotope concentration chart to determine a birth date of said biomolecule (see Methods section – Age determination, pages 275-276).

16. Claims 1, 4, 11, 17-18, 22-24, and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Kalish et al. (Marine Biology, 1997). As discussed in the 35 U.S.C. 112, second paragraph, rejection above, "said DNA" recited in step (c) of claim 1

lacks antecedent basis. Accordingly, claim 1 has been interpreted as a method of determining a birth date of any biomolecule, not limited to DNA.

With regard to claim 1, Kalish et al. teach a method for determining a birth date of a biomolecule comprising:

a. Providing a biomolecule (see abstract & Materials and methods, page 558)

b. Determining a delta ^{14}C value of the biomolecule (see abstract and Materials & methods, page 558)

c. Determining a birth date of said biomolecule by comparing the delta ^{14}C value of said biomolecule with a calibration delta ^{14}C chart to determine a birth date of said biomolecule (see Materials and Methods, page 558).

With regard to claim 4, the biomolecule of Kalish et al. is derived from the otoliths of the blue grenadier, and therefore meets the limitation that the biomolecule is an animal, plant or virus, or part thereof.

With regard to claim 11, Kalish et al. determine the delta ^{14}C value using an accelerator mass spectrometer (see Materials & methods, page 558).

With regard to claim 17, Kalish et al. teach a method of determining the birth date of a biomolecule in an organism population, comprising:

(a) Collecting a sample of said biomolecule from an organism population; wherein said biomolecule is purified away from other carbon-containing molecules of said organism population (see Materials and methods).

(b) determining a delta ^{14}C value of the carbon atoms in said biomolecule (see Materials and methods)

(c) comparing the delta ^{14}C value with a calibration delta ^{14}C chart to determine a birth date of said biomolecule (see Materials and methods).

With regard to claim 18, the method of Kalish et al. uses the blue grenadier (a fish), thereby meeting the instant limitation that the organism is an animal, plant or virus (see abstract).

With regard to claim 22, Kalish et al. determine the delta ^{14}C value using an accelerator mass spectrometer (see Materials and methods).

With regard to claim 23, the method of Kalish et al. includes calculating a birth date of an animal from the birth date of the biomolecule (see abstract).

With regard to claim 24, Kalish et al. determine the age of the blue grenadier based on counting the number of annual increments present in the otoliths (see Materials and methods), thereby meeting the instant limitation that the method include a step of measuring a second indicator of cell age.

With regard to claim 31, Kalish et al. teach a method of determining a birth date of a biomolecule, comprising:

(a) providing a biomolecule (see abstract)

(b) determining an isotope concentration of said biomolecule (see abstract and Materials & methods)

(c) determining a birth date of said biomolecule by comparing the isotope concentration with a calibration isotope concentration chart to determine a birth date of said biomolecule (see abstract and Materials & methods).

17. Claims 1, 3-5, 7-8, 11, 17-19, and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Bonnichsen et al. (Journal of Archaeological Science, July 2001). As discussed in the 35 U.S.C. 112, second paragraph, rejection above, "said DNA" recited in step (c) of claim 1 lacks antecedent basis. Accordingly, claim 1 has been interpreted as a method of determining a birth date of any biomolecule, not limited to DNA.

With regard to claim 1, Bonnichsen et al. teach a method for determining a birth date of a biomolecule comprising:

a. Providing a biomolecule (see abstract)

b. Determining a delta ^{14}C value of the biomolecule (see abstract)

c. Determining a birth date of said biomolecule by comparing the delta ^{14}C value of said biomolecule with a calibration delta ^{14}C chart to determine a birth date of said biomolecule (see abstract).

With regard to claim 3, the biomolecule of Bonnichsen et al. is isolated from a tissue, specifically skin (see abstract).

With regard to claim 4, the biomolecule of Bonnichsen et al. originates from an animal, a plant, or a virus (see abstract).

With regard to claim 5, the biomolecule of Wild et al. is isolated from a purified cell population (see abstract).

With regard to claim 7, Bonnichsen et al. teach the use of dating hair samples which contain DNA, thereby meeting the limitation that the biomolecule is DNA (see abstract).

With regard to claim 8, Bonnichsen et al. teach that DNA is isolated from a tissue, a cell line or purified cell population, by removal of the hair from the skin tissue (see abstract).

With regard to claim 11, Bonnichsen et al. determine the delta ^{14}C value using an accelerator mass spectrometer (see abstract).

With regard to claim 17, Bonnichsen et al. teach a method of determining the birth date of a biomolecule in an organism population, comprising:

(a) Collecting a sample of said biomolecule from an organism population; wherein said biomolecule is purified away from other carbon-containing molecules of said organism population (see Materials and methods).

(b) determining a delta ^{14}C value of the carbon atoms in said biomolecule (Results section)

(c) comparing the delta ^{14}C value with a calibration delta ^{14}C chart to determine a birth date of said biomolecule (see Results section).

With regard to claim 18, the method of Bonnichsen et al. uses the desert bighorm sheep, thereby meeting the instant limitation that the organism is an animal, plant or virus (see abstract).

With regard to claim 19, Bonnichsen et al. use hair samples which contain DNA, thereby meeting the limitations of the instant claim (see abstract).

With regard to claim 22, Bonnichsen et al. determine the delta ^{14}C value using an accelerator mass spectrometer (see abstract).

18. Claims 1, 3-5, 11, 17-18 and 20-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Hedges et al. (Radiocarbon, 1995). As discussed in the 35 U.S.C. 112, second paragraph, rejection above, "said DNA" recited in step (c) of claim 1 lacks antecedent basis. Accordingly, claim 1 has been interpreted as a method of determining a birth date of any biomolecule, not limited to DNA.

With regard to claim 1, Hedges et al. teach a method for determining a birth date of a biomolecule comprising:

a. Providing a biomolecule (see abstract)

b. Determining a delta ^{14}C value of the biomolecule (see abstract)

c. Determining a birth date of said biomolecule by comparing the delta ^{14}C value of said biomolecule with a calibration delta ^{14}C chart to determine a birth date of said biomolecule (see Table 1, page 288, and note that presentation of the difference between the percentage of ^{14}C observed and expected inherently implies the use of a calibration delta ^{14}C chart).

With regard to claim 3, the biomolecule of Hedges et al. is isolated from a tissue, specifically connective tissue (bone) (see abstract).

With regard to claim 4, the biomolecule of Hedges et al. originates from an animal, a plant, or a virus (see abstract).

With regard to claim 5, the biomolecule of Hedges et al. is isolated from a purified cell population (see abstract).

With regard to claim 11, Hedges et al. determine the delta ^{14}C value using an accelerator mass spectrometer (see Introduction, page 285).

With regard to claim 17, Hedges et al. teach a method of determining the birth date of a biomolecule in an organism population, comprising:

(a) Collecting a sample of said biomolecule from an organism population; wherein said biomolecule is purified away from other carbon-containing molecules of said organism population (page 287).

(b) determining a delta ^{14}C value of the carbon atoms in said biomolecule (page 287)

(c) comparing the delta ^{14}C value with a calibration delta ^{14}C chart to determine a birth date of said biomolecule (page 287).

With regard to claim 18, the method of Hedges et al. uses samples from mammoth, rhino, hyena, horse, etc, thereby meeting the instant limitation that the organism is an animal, plant or virus (see Table 1, page 288).

With regard to claim 20, the biomolecule used by Hedges et al. is tooth enamel from an animal (see abstract).

With regard to claim 21, an animal used by Hedges et al. is a horse (see Table 1), thereby meeting the limitation that the animal be selected from the group consisting of a human, a horse, a pig, a cow, a rabbit, a dog, a rat and a mouse.

With regard to claim 22, Hedges et al. determine the delta ^{14}C value using an accelerator mass spectrometer (see Introduction, page 285).

With regard to claim 23, Hedges et al. calculate a birth date of an animal from the birth date of the biomolecule (see abstract and Table 1).

Claim Rejections - 35 USC § 103

20. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

21. Claims 9, 10, and 14-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Robertson et al. (Journal of Radioanalytical and Nuclear Chemistry, August 2001) in view of Sheehy (Archives of Gerontology and Geriatrics, May-June 2002) and further in view of Robertson et al. (Neurobiology of Aging, Jan. 2002).

Robertson et al. (Journal of Radioanalytical and Nuclear Chemistry, August 2001) teach the method of claim 1, as discussed above.

Robertson et al. (Journal of Radioanalytical and Nuclear Chemistry, August 2001) do not teach that the cell from which the biomolecule is derived is analyzed by a secondary birth dating method before step (b) of the method of claim 1, where the secondary birth dating method comprising measuring the histone acetylation level, the DNA oxidation level, or the cellular lipofuschin level using a fluorescence activated cell sorter.

Robertson et al. discuss in a later publication (Neurobiology of Aging, Jan. 2002) the reduced precision inherent in dating neurofibrillary tangles (NFTs) and senile plaques (SPs) obtained from a bulk sample and describe a modification to the original method (cited above, Journal of Radioanalytical and Nuclear Chemistry, 2001) wherein further dissection of the cerebellum is employed to eliminate regional differences between the NFT and SP populations, thus improving the initial homogeneity of the sample to be dated (see Discussion, page 184).

Sheehy teaches a flow-cytometric method for quantification of cellular neurolipofuschin as an improved tool for age determination. Terminal medullae from whole eyestalks from the European lobster, *Homarus gammarus*, were homogenized

and subjected to fluorescence activated cell sorting (FACS) analysis, where the sorting was based on the cellular lipofuschin level (see Materials & methods, pages 236-237). Sheehy further compares this new method involving FACS analysis with previous histological and biochemical methods of age determination based on cellular lipofuschin levels, pointing out that FACS analysis offers a faster way to determine age (see abstract). Sheehy also points out that neurolipofuschin-based age determination is more accurate than the conventional dating method for lobsters based on growth rate extrapolation (page 244).

With regard to claims 9 and 10, Sheehy teaches purification using a secondary birth dating method performed using a fluorescence activated cell sorter where sorting is based on the histone acetylation level, DNA oxidation level, or cellular lipofuschin level (see abstract).

With regard to claims 14-16, Sheehy teaches the analysis of a biomolecule derived from a cell, by a secondary birth dating method comprising measuring the histone acetylation level, the DNA oxidation level, or the cellular lipofuschin level using a fluorescence activated cell sorter (see abstract and pages 236-237).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to use the method of age determination by FACS analysis based on cellular lipofuschin level described by Sheehy in the carbon-14 dating method of Robertson et al. (Journal of Radioanalytical and Nuclear Chemistry, 2001), because Sheehy states that such a method is a fast and efficient way to sort a purified cell population (see abstract). The discussion of the need for improved sample

homogeneity in the subsequent publication of Robertson et al. (Neurobiology of Aging, Jan. 2002) would have further motivated the ordinary artisan to incorporate the quick and efficient lipofuschin-based FACS analysis described by Sheehy into the method of Robertson et al. (Journal of Radioanalytical and Nuclear Chemistry, 2001) to improve the homogeneity of the NFT and SP populations prior to radiocarbon dating and also to potentially eliminate the need for the more time-consuming practice of further cerebellum dissection prior to dating. One of ordinary skill would have enjoyed a reasonable expectation of success in combining the methods of Robertson et al. and Sheehy, because the method of Sheehy is performed using bulk tissue homogenates from a neuronal cell population. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of invention to practice the lipofuschin-based FACS analysis of Sheehy in the method of Robertson et al., thus resulting in the practice of the instantly claimed invention.

22. Claims 24 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Robertson et al. in view of Sheehy (Archives of Gerontology and Geriatrics, May-June 2002).

Robertson et al. teach the method of claim 17, as discussed above.

Sheehy teaches a flow-cytometric method for quantification of cellular neurolipofuschin as an improved tool for age determination as discussed above.

With regard to claims 24 and 25, Sheehy measure a second indicator of cell age (cellular lipofuschin levels – which are a second indicator relative to conventional age

determination based on growth rate extrapolation) selected from the group consisting of histone acetylation levels, DNA oxidation levels, or cellular lipofuschin levels (see abstract).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to incorporate the method of age determination using FACS analysis based on cellular lipofuschin level described by Sheehy into the carbon-14 dating method of Robertson et al., because Sheehy states that this method is a fast and reasonably accurate method of dating a population of cells (see abstract and page 244). As discussed above Robertson et al. recognize the inaccuracies resulting from dating NFTs and SPs resulting from a bulk sample, thereby leading the artisan of ordinary skill to seek a method of improving sample homogeneity and also an additional method of dating. The method of Sheehy offers both improved sample homogeneity and an independent age determination, thus providing the ordinary artisan with a relatively convenient improvement to the method of Robertson et al. Therefore, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to practice lipofuschin-based FACS analysis before obtaining a carbon-14 dating-based age determination of biomolecules, thus resulting in the practice of the instantly claimed invention with a reasonable expectation of success.

23. Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hellerstein in view of Robertson et al. (U.S. Patent No. 6,010,846).

Hellerstein teaches a method of measuring cell proliferation rates in vivo and in vitro comprising measuring DNA synthesis by detection of a stable isotope label incorportated into newly synthesized DNA (see abstract and column 2, lines 40-49). With regard to claim 26, Hellerstein teaches use of this method for determining the effect of a candidate agent on cell proliferation (column 4, lines 38-50). Hellerstein does not teach the use of the method of the instant claim 1 to determine a first birth date of a first cell sample from a tissue type in an animal before administration of the candidate agent.

Robertson et al. disclose the method of claim 1, as discussed above.

One of ordinary skill in the art at the time of invention would have been motivated to combine the methods of Robertson et al. and Hellerstein in order to obtain an additional independent measure of cell proliferation in response to a candidate agent. Robertson et al. teach that bomb-pulse carbon-14 AMS measurements of NFTs and SPs give an accurate age determination of these biomolecules, and the ordinary artisan would have been motivated to incorporate such AMS measurements of cell age pre and post-administration of the candidate agent, because doing so would provide a measure this agent's effect on cell proliferation independent of the (perhaps more variable) measurement of a co-administered stable isotope label to be incorporated into newly synthesized DNA. Therefore, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to practice carbon-14 dating as described by Robertson et al. in the method of Hellerstein, thus resulting in the practice of the instantly claimed method with a reasonable expectation of success.

24. Claims 26-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Czeh et al. in view of Robertson et al. (PNAS, October 2001).

Czeh et al. teach a method of treating depression with tianeptine, based on its ability to prevent the decreased cell proliferation observed in depression. Tianeptine was administered to tree shrews during a period of induced social stress. At the conclusion of this period, BrdU (a marker used to identify dividing cells) was injected into the animals and quantified to determine the effect of tianeptine on cell proliferation in the hippocampus (a CNS tissue type). See the Experimental Procedure and Histological procedure sections of the Materials and Methods (page 12797) and also the second section of the Results (page 12798).

With regard to claim 26, Czeh et al. teach a method of determining the effect of a candidate agent on cell proliferation comprising, administration of a candidate agent (tianeptine) and detecting newly dividing cells via BrdU labeling, thus determining the effect of the candidate agent on cell proliferation (Experimental Procedure and Histological procedure sections of the Materials and Methods, page 12797).

With regard to claim 27, the method of Czeh et al. monitors the effects of tianeptine in the hippocampus, a CNS tissue type (see the second section of the Results, page 12798).

With regard to claim 28, Czeh et al. teach a method of determining the effect of a treatment on cell proliferation, comprising: inducing an event in an animal (social stress, see Experimental procedure, page 12797) and determine the effect of the event on cell

proliferation by detecting the presence of BrdU-labeled newly dividing cells (See the Experimental Procedure and Histological procedure sections of the Materials and Methods (page 12797) and also the second section of the Results (page 12798).

With regard to claim 29, the treatment (induced social stress) used in the method of Czeh et al. is selected from the group consisting of trauma, an induced disorder, a surgical procedure and the administration of an agent (see Experimental procedure, page 12797).

With regard to claim 30, the treatment of Czeh et al. induces or affects a neurological disorder (depression, see abstract).

Robertson et al. teach the method of claim 1, as discussed above.

It would have been prima facie obvious to one of ordinary skill in the art at the time of invention to incorporate the method of Robertson et al. into the method of Czeh et al., in order to obtain an additional independent measure of cell proliferation in response to a candidate agent. Robertson et al. teach that bomb-pulse carbon-14 AMS measurements of NFTs and SPs give an accurate age determination of these biomolecules, and the ordinary artisan would have been motivated to incorporate such AMS measurements of cell age pre and post-administration of the candidate agent, because doing so would provide a measure of the agent's effect on cell proliferation independent of the (perhaps more variable) measurement BrdU-labeled cells. Therefore, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to practice carbon-14 dating as described by Robertson et al. in the

method of Czeh et al., thus resulting in the practice of the instantly claimed method with a reasonable expectation of success.

25. Claims 26-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Madsen et al. (Biological Psychiatry, 2000) in view of Robertson et al.

Madsen et al. teach a method of treating depressive disorders by using electroconvulsive therapy to increase neurogenesis. Briefly, electroconvulsive seizures were delivered to rats at least once, BrdU was injected into the rats, and newly dividing cells labeled with BrdU were detected in the brain tissue and compared to control brain tissue to determine the effect of the electroconvulsive therapy on cell proliferation. See Methods and Materials and Results section (pages 1044 & 1046).

With regard to claim 26, Madsen et al. teach a method of determining the effect of a candidate agent on cell proliferation comprising, administration of a candidate agent (electroconvulsive therapy) and detecting newly dividing cells via BrdU labeling, thus determining the effect of the candidate agent on cell proliferation (page 1044 & 1046).

With regard to claim 27, the method of Madsen et al. monitors the effects of electroconvulsive therapy in the brain, a CNS tissue type (page 1044).

With regard to claim 28, Madsen et al. teach a method of determining the effect of a treatment on cell proliferation, comprising: inducing an event in an animal (electroconvulsive therapy, page 1044) and determining the effect of the event on cell proliferation by detecting the presence of BrdU-labeled newly dividing cells (page 1044 & 1046).

With regard to claim 29, the treatment (electroconvulsive therapy) used in the method of Madsen et al. is selected from the group consisting of trauma, an induced disorder, a surgical procedure and the administration of an agent (page 1044).

With regard to claim 30, the treatment of Madsen et al. induces or affects a neurological disorder (depression, page 1043).

It would have been prima facie obvious to one of ordinary skill in the art at the time of invention to incorporate the method of Robertson et al. into the method of Madsen et al., in order to obtain an additional independent measure of cell proliferation in response to a candidate agent. Robertson et al. teach that bomb-pulse carbon-14 AMS measurements of NFTs and SPs give an accurate age determination of these biomolecules, and the ordinary artisan would have been motivated to incorporate such AMS measurements of cell age pre and post-administration of the candidate agent, because doing so would provide a measure of the agent's effect on cell proliferation independent of the (perhaps more variable) measurement BrdU-labeled cells. Therefore, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to practice carbon-14 dating as described by Robertson et al. in the method of Madsen et al., thus resulting in the practice of the instantly claimed method with a reasonable expectation of success.

Conclusion

26. No claims are currently allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Angela Bertagna whose telephone number is (571) 272-8291. The examiner can normally be reached on M-F 7:30-5 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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12/16/2005

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12/15/05